Post-treatment renin status and cardiovascular, renal, and mortality outcomes in medically treated primary aldosteronism: a systematic review and meta-analysis

Sho Katsuragawa, Minh V Le, Peter J Fuller, Jun Yang

Summary

Background Renin suppression persists in many patients with primary aldosteronism despite targeted medical treatment, which might indicate suboptimal mineralocorticoid receptor blockade. This study systematically reviewed the evidence for an association between post-treatment renin status and cardiovascular, renal, and mortality outcomes in medically treated primary aldosteronism.

Methods For this systematic review and meta-analysis, MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Web of Science were searched from database inception up to May 5, 2025, for studies that investigated the association between post-treatment renin status and clinical outcomes among medically treated patients with primary aldosteronism. The primary outcomes were the incidence of cardiovascular events, renal events, and all-cause mortality. Risk-of-bias was assessed using the Quality in Prognostic Studies (QUIPS) tool. Random-effects models were employed to estimate pooled hazard ratios (HRs) with 95% CIs. The protocol was pre-registered on PROSPERO (CRD42024598737).

Findings 3814 records were identified and 24 studies involving 6621 patients with primary aldosteronism on mineralocorticoid receptor antagonists were eligible and included, of which five studies contributed data to the meta-analyses of the primary outcomes. Most studies used plasma renin activity with a cut-off of 1·0 ng/mL per h to classify post-treatment renin as suppressed or unsuppressed. For the primary meta-analysis, individuals with unsuppressed post-treatment renin had a significantly lower risk of cardiovascular events compared with those with suppressed renin (pooled HR 0·43 [95% CI 0·23–0·80], I^2=37%; four studies, 874 patients, low certainty of evidence). A subgroup meta-analysis demonstrated that unsuppressed post-treatment renin was associated with a significantly lower risk of cardiovascular events after 5 or more years of follow-up (pooled HR 0·33 [95%CI, 0·19–0·57], I^2=0%, three studies, 754 patients; moderate certainty). No significant association was found with renal outcomes (pooled HR 0·95 [95% CI 0·51–1·77], two studies, I^2=0%, very low certainty). One study reported a lower risk of all-cause mortality in patients with unsuppressed post-treatment renin than those with suppressed post-treatment renin (HR 0·29 [95% CI 0·09–0·98], 201 patients; low certainty). None of the studies were judged to have low risk of bias across all QUIPS domains, but many studies had high risk of bias in Domain 5 (bias due to confounding).

Interpretation The association between unsuppressed renin following medical therapy for primary aldosteronism and reduced risk of cardiovascular events and all-cause mortality suggests that renin normalisation might serve as a therapeutic target. Prospective studies are required to formally confirm that medication titration to normalise renin improves clinical outcomes.

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Centre for Endocrinology and Reproductive Health, Hudson Institute of Medical Research, Clayton, VIC, Australia (S Katsuragawa MD, Prof P J Fuller PhD, J Yang PhD); **Department of Molecular and Translational Science, Monash University, Clayton, VIC, Australia** (S Katsuragawa, J Yang); **Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Parkville, VIC, Australia** (M V Le MD); **Department of Diabetes and Endocrinology, Western Health, St Albans, VIC, Australia** (M V Le)

Correspondence to: Dr Jun Yang, Centre for Endocrinology and Reproductive Health, Hudson Institute of Medical Research, Clayton, VIC 3168, Australia **jun.yang@hudson.org.au**

Introduction

Primary aldosteronism is the main cause of secondary hypertension, characterised by excess aldosterone production with renin suppression.[1] The high prevalence of primary aldosteronism and its increased risk of cardiovascular and renal damage, compared with essential hypertension, emphasises the importance of optimal treatment for primary aldosteronism.[2–7] Treatment options include unilateral adrenalectomy for lateralising primary aldosteronism, or targeted medical therapy with mineralocorticoid receptor antagonists (MRAs) or epithelial sodium channel (ENaC) inhibitors.[1,8] The majority of primary aldosteronism cases are consistently found to be non-lateralising and non-neoplastic, which can benefit from medical therapy.[2,8]

In addition to normalisation of blood pressure and serum potassium, normalisation of post-treatment renin with targeted medical treatment is also recommended by guidelines and expert panels.[1,9–13] The Primary Aldosteronism Medical Treatment Outcome (PAMO) criteria were recently proposed by international

Research in context

Evidence before this study

Primary aldosteronism is the leading cause of secondary hypertension and confers disproportionately high risks of adverse cardiovascular and renal outcomes. Most patients with primary aldosteronism are treated medically with mineralocorticoid receptor antagonists (MRAs), but there is uncertainty around optimal treatment targets. Renin has been proposed as a key biomarker for monitoring treatment efficacy, reflecting the degree of mineralocorticoid receptor blockade. Guidelines and expert panels suggest normalising post-treatment renin status, typically defined as plasma renin activity 1·0 ng/mL per h or greater or direct renin concentration 10 mIU/L or greater, to improve cardiovascular and renal outcomes. This suggestion is based on observational studies demonstrating that unsuppressed renin after medical treatment is associated with lower cardiovascular risk. However, other studies have reported no significant association between post-treatment renin status and cardiovascular and renal outcomes. This discrepancy highlights the need for a systematic review and evidence synthesis. Thus, we systematically reviewed articles in which the association between post-treatment renin status and cardiovascular and renal outcomes, mortality, and other surrogate parameters among medically treated patients with primary aldosteronism was reported. We conducted a comprehensive search on MEDLINE, Embase, CENTRAL, and Web of Science from database inception until May 5, 2025 with no language restrictions, using the search terms: "Hyperaldosteronism" AND ("mineralocorticoid receptor antagonists" OR "epithelial sodium channel blockers") AND "Renin".

Added value of this study

We identified 24 studies involving 6621 patients with primary aldosteronism on MRA therapy; 16 of these (3177 patients) were included in meta-analyses. Most studies had moderate to high risk of bias due to confounding. Our meta-analysis found that unsuppressed post-treatment renin was associated with a lower risk of cardiovascular events in studies with 5 or more years of follow-up. No association was found with renal events. One study reported a lower risk of all-cause mortality with unsuppressed renin. To our knowledge, our study is the first to systematically review and synthesise the evidence on the association between post-treatment renin status and clinical outcomes in patients with primary aldosteronism receiving targeted medical therapy. Our findings support current expert recommendations that normalisation of post-treatment renin should be targeted to mitigate the risk of cardiovascular events. Meta-analyses of surrogate parameters showed that unsuppressed post-treatment renin was associated with lower blood pressure, further supporting the prognostic value of aiming for renin normalisation.

Implications of all the available evidence

Our findings reinforce the clinical importance of post-treatment renin as a biomarker to assess the efficacy of medical treatment for primary aldosteronism, particularly for cardiovascular protection. However, limitations related to confounding and sparse data on renal outcomes warrant caution. Prospective trials are warranted to confirm whether medication titration improves clinical outcomes through normalisation of post-treatment renin.

experts to evaluate the response to targeted medical therapy.[14] The normalisation of post-treatment renin, defined as plasma renin activity (PRA) of 1·0 ng/mL per h or greater, or direct renin concentration of 10 mIU/L or greater, has been recommended as a marker of biochemical response within the PAMO criteria. The evidence for this recommendation stems from several observational studies that demonstrated favourable cardiovascular and renal prognoses in patients with medically treated primary aldosteronism with unsuppressed post-treatment renin compared with those with persistent renin suppression.[15–18] However, conflicting findings have also been reported, in which no associations between post-treatment renin and cardiovascular and renal outcomes were observed.[19,20] Additionally, there is little guidance on the optimal upper limit for post-treatment renin during medical treatment. This highlights the need for a synthesised body of evidence in this field. We aimed to systematically review and synthesise the available evidence on the association of post-treatment renin status with clinical outcomes among patients with primary aldosteronism medically treated with MRAs or ENaC inhibitors.

Methods

Search strategy and selection criteria

We conducted a systematic review and meta-analysis of studies that examined the association between post-treatment renin status and clinical outcomes among patients with primary aldosteronism treated with the targeted medical therapy. The review adhered to the PRISMA guidelines, the Cochrane Handbook, and the guide by experts in the field of systematic review and meta-analysis of prognostic factor studies, to ensure methodological rigour.[21–23] The protocol was registered with PROSPERO before commencement (ID: CRD42024598737).

The studies included in this review were cohort studies, case-control studies, cross-sectional studies, and prospective interventional studies that involved patients with primary aldosteronism on MRAs or ENaC inhibitors. Case reports, case series, conference abstracts, and thesis were excluded. The exposure of interest was post-treatment renin status which was measured after initiation of the targeted medical treatment. The primary outcomes were the incidence of cardiovascular events, renal events, and all-cause mortality. The secondary

outcomes were surrogate parameters for the primary outcomes (echocardiographic parameters, vascular functions, estimated glomerular filtration rate [eGFR], urinary albumin excretion, and blood pressure), targeted medication (proportion of spironolactone and dose of MRAs) and adverse clinical outcomes that might be related to supraphysiological post-treatment renin status due to over titration of the targeted medication (eg, hypotension, hyperkalaemia, and gynaecomastia).

A comprehensive search of four electronic databases, MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, were conducted for eligible studies published in any language from database inception up to May 5, 2025. The full search strategy for each database is presented in the appendix (pp 3–5). References of studies included in our review were also hand-searched for potentially eligible studies. Grey literature sources or trial registries were not searched. Two reviewers (SK and MVL) independently screened the titles and abstracts of all records identified through the search, followed by full-text screening for the final inclusion in this review. Disagreement in screenings between the reviewers were resolved via discussion or consultation with a third reviewer (JY). For literature written in other languages than English, translation apps (eg, Google Translate) were used. We contacted authors of included studies for further information when necessary.

Data analysis

Data extraction and risk of bias assessment of studies were independently conducted by two reviewers (SK and MVL) using the Covidence software.[24] Extracted data included study and patient characteristics, post-treatment renin status, outcomes, and effect estimates. For incidence outcomes, we collected the total number of patients and events, adjusted hazard ratios (HR) with corresponding 95% CIs, and covariates. We also collected the number of total patients and cases for proportion outcomes, and mean and SD for continuous outcomes. Risk of bias for each study was assessed using the Quality in Prognostic Studies (QUIPS) tool.[25] For Domain 5 of the QUIPS tool which assesses risk of bias due to confounding, we prespecified the following factors as important confounders that are suggested by previous literature to affect both the exposure (ie, post-treatment renin status) and the outcome (ie, cardiovascular events): age,[26,27] sex,[26,27] blood pressure,[18,27] BMI,[18,27–29] serum potassium or the presence of hypokalaemia,[18,30] renin status, and plasma aldosterone level before initiation of targeted medical treatment.[15,31,32] Studies were judged as having low risk of bias in Domain 5 if all confounders were accounted for in the analyses or design (eg, matching), high risk if four or more of the confounders were unaccounted for, and moderate risk otherwise. Disagreements between the two reviewers were resolved through discussion with a third reviewer (JY).

Meta-analyses were performed to estimate pooled HRs for incidence outcomes (cardiovascular and renal events), pooled odds ratios (ORs) for proportion outcomes (presence of left ventricular hypertrophy assessed with echocardiography and use of spironolactone), and mean differences for continuous outcomes (eGFR, blood pressure, and dose of MRAs) when more than one study reported these outcomes by different categories of post-treatment renin status (eg, unsuppressed *vs* suppressed). Among studies eligible for inclusion in the meta-analyses for systolic and diastolic blood pressure, two studies originated from overlapping cohorts.[33,34] To avoid duplication, we included only the study with the larger sample size.[33] As a sensitivity analysis, we repeated the meta-analysis replacing the larger study with the smaller one.[34] Pooled estimates were presented with their 95% CI. To allow for a meta-analysis of MRA dose, eplerenone and esaxerenone doses were converted to spironolactone equivalents by dividing by 2 and multiplying by 10, respectively, as previously described.[15,18,35,36] When studies reported medians and IQRs instead of means and SDs, conversions were performed using Cochrane-suggested formulas (appendix p 6).[22,37] Random-effects models with the inverse-variance method were used for meta-analyses, and heterogeneity across studies was quantified with the I^2 statistic.[22] Potential publication bias and small-study effects were assessed using funnel plots, and Egger's test was performed in meta-analyses with ten or more studies.[38] When heterogeneity ($I^2 \geq 30\%$) across studies was observed in a meta-analysis, subgroup analyses stratified by the study duration (≥5 years or <5 years), post-treatment renin cut-off values defining unsuppressed or suppressed status (PRA ≤0·6 ng/mL per h, 0·6 <PRA <1·4 ng/mL per h, or PRA ≥1·4 ng/mL per h), and study region (Asia or non-Asia) were conducted to explore a possible cause of the heterogeneity. According to the latest Endocrine Society guideline,[39] PRA of 1·0 ng/mL per h is considered equivalent to a direct renin concentration of 8·2 mIU/L and 5·2 pg/mL. To confirm the robustness of the pooled estimate, we performed sensitivity analyses for the incidence of cardiovascular events by excluding studies with high risk of bias in Domain 5 of the QUIPS tool. Additionally, a leave-one-out sensitivity meta-analysis was performed for the incidence of cardiovascular events to evaluate the robustness of the main meta-analysis and explore potential studies with substantial influence on the pooled estimate.

All statistical analyses including meta-analyses were performed using the meta package in R software version 4.3.2. The certainty of evidence for each meta-analysis was assessed using the Grading of Recommendations Assessment, Development, and Evaluation framework and graded as either high, moderate, low, or very low.[38,40] As all outcomes were derived from observational data, the starting level of certainty was low,

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with further downgrades by one or two levels based on risk of bias, inconsistency, indirectness, imprecision, and publication bias. One level upgrading of the certainty of evidence was considered for large effect sizes, evidence of dose response, and confounding likely to reduce the observed effect.[38,40]

Role of the funding source

There was no funding source for this study.

Results

Through the comprehensive search, we identified 3814 records from the four databases and references of included studies. After removing 1290 duplicates, 2524 titles and abstracts were screened, and 410 full-text articles were assessed for eligibility. A total of 24 studies involving 6621 individuals with primary aldosteronism treated with targeted medication were included in our review.[14–20,33,34,36,41–54] Of these, 16 studies were eligible for inclusion in the meta-analyses (figure 1),[14,15,18–20,33,34,36,41–43,45,50,51,53,54] among which five studies contributed to the meta-analyses for the primary outcomes.[15,19,20,45,53]

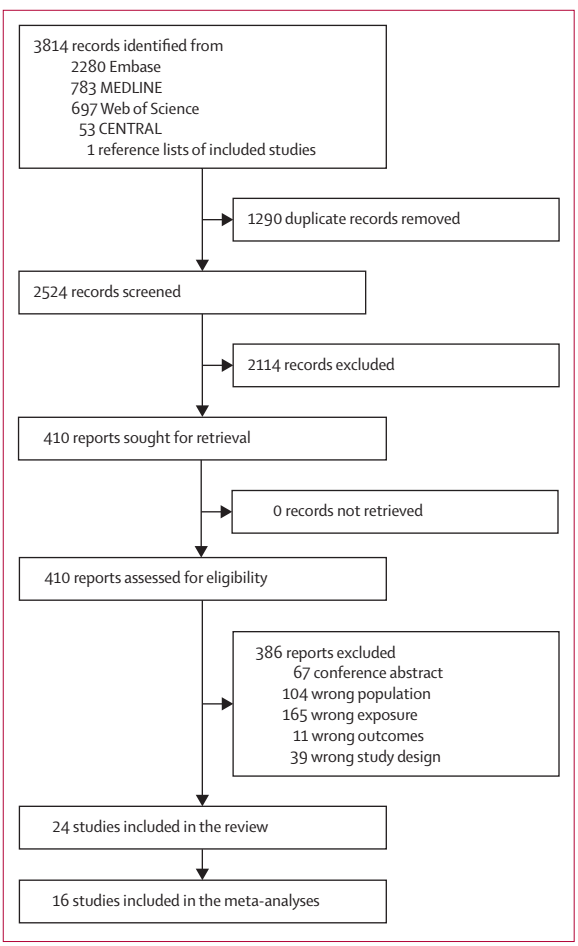

Figure 1: **Study selection**
CENTRAL= Cochrane Central Register of Controlled Trials.

Among the 24 studies, 21 were cohort studies,[15–20,33,34,36,41–49,52,53] and three were single-arm interventional studies in which associations between post-treatment renin status and relevant outcomes were analysed (table).[50,51,54] Ten studies were conducted in Japan,[18,44,46–52,54] four in the USA,[15,16,20,36] three in Taiwan,[42,43,53] two in Germany,[33,34] and one in each of China,[45] Norway,[41] Singapore,[17] and Spain.[19] One study used an international cohort involving 31 medical centres from 17 countries.[14] There was some overlap in the cohorts used in the included studies: the Japan Primary Aldosteronism Study and the Japan Rare/Intractable Adrenal Diseases Study registry was used in three studies,[44,47,49] a research registry at Brigham and Women's Hospital, Massachusetts General Hospital, and their affiliated partner hospitals in three studies,[15,16,20] the Taiwan Primary Aldosteronism Investigation database in three studies,[42,43,53] the primary aldosteronism database at Yokohama Rosai Hospital in two studies,[18,52] and the German Conn's Registry in two studies.[33,34] MRAs were the predominant treatment across all the studies.[15–20,33,34,36,41–54] Only one study included ENaC inhibitors, although MRAs remained the predominant therapy.[14] Post-treatment renin status was assessed using PRA in 13 studies,[15–18,20,42,43,45,46,50–53] direct renin concentration in three studies,[33,34,54] and both markers in four studies.[14,19,36,41] Most studies that measured PRA used 1·0 ng/mL per h as the cut-off to classify post-treatment renin as unsuppressed or suppressed.[14–20,36,43,45,46,50–52] The cut-off values for direct renin concentration varied by studies ranging from 4·4 mIU/L[41] to 8·0 pg/mL.[36] One study used post-treatment PRA as a continuous variable,[44] and three studies analysed the association between changes in PRA (pre-targeted *vs* post-targeted medical treatment) and outcomes.[47–49] No studies examined the association between supraphysiological post-treatment renin and the outcomes. Risk of bias assessment is shown in the appendix (p 12). None of the studies were judged to have low risk of bias across all QUIPS domains, with many studies showing high risk of bias in Domain 5 (bias due to confounding).

A meta-analysis of the incidence of cardiovascular events demonstrated that patients with unsuppressed post-treatment renin had a significantly lower risk compared with those with suppressed renin (pooled HR 0·43 [95% CI 0·23–0·80], I^2=37%; four studies, 874 patients, low certainty of evidence; figure 2, appendix pp 8–9, 13).[15,19,45,53] To investigate the mild to moderate heterogeneity (I^2=37%), a subgroup analysis stratified by follow-up duration was conducted. This subgroup analysis demonstrated that among patients with follow-up of 5 years or more, unsuppressed post-treatment renin was associated with a reduced risk of cardiovascular events (pooled HR 0·33 [95% CI 0·19–0·57], I^2=0%, three studies, 754 patients; moderate certainty of evidence; figure 3, appendix pp 8–9).[15,45,53] By contrast, no significant association was found for patients with less than 5 years of follow-up (p value for subgroup

	Number of participants on MRA analysed	Key characteristics of medically treated PA population*	Cut-off for UNS or SUP	Time between targeted medication initiation and post-treatment renin measurement	Follow-up period	Reported outcomes	aHR (95% CI) for the primary outcomes (UNS *vs* SUP)
Aune 2022;[41] cohort study, Norway	43	Age: mean 58 (SD 10) years; female: 10 (23%); unilateral PA: 1 (2%); PRA before treatment: median 0·3 (IQR 0·1–0·7) ng/mL per h; PRA after treatment: median 0·7 (IQR 0·2–5·9) ng/mL per h	PRA 0·5 ng/mL/h or DRC 4·4 mIU/L	1 year	Cross-sectional analysis	Echocardiographic parameters	The primary outcomes were not measured
Chen 2023;[42] cohort study, Taiwan	190 (84 with UNS, 106 with SUP)	UNS group: age: mean 53 (SD 12) years; female: 37 (44%); unilateral PA: 22 (26%); PRA before treatment: mean 0·5 (SD 0·8) ng/mL/h; PRA after treatment: mean 4·2 (SD 3·4) ng/mL/h; SUP group: age: mean 56 (SD 12) years; female: 61 (57%); unilateral PA: 41 (39%); PRA before treatment: mean 0·3 (SD 0·5) ng/mL/h; PRA after treatment: mean 0·4 (SD 0·7) ng/mL/h	PRA 1·5 ng/mL/h	1 year	Cross-sectional analysis	Vascular function, blood pressure	The primary outcomes were not measured
Chen 2024;[43] cohort study, Taiwan	59	Age: mean 58 (SD 12) years; female: 30 (51%); unilateral PA: 59 (100%); PRA before treatment: mean 0·2 (SD 0·6) ng/mL/h	PRA 1·0 ng/mL/h	1 year	Cross-sectional analysis	Vascular function	The primary outcomes were not measured
Haze 2021;[44] cohort study, Japan	1247	Age: mean 54 (SD 11) years; female: 666 (53%); history of cardiovascular disease 72 (5·8%); PRA before treatment: mean 0·4 (SD 0·3) ng/mL/h; PRA after treatment: mean 1·5 (SD 3·6) ng/mL/h	Continuous PRA	0–6 months	Median 3·1 (1·1–5·1) years	Composite incidence of cardiovascular events and mortality	aHR 0·75 (95% CI, 0·22 to 2·54) for cardiovascular events for 3·2 ng/mL/h increase in post-treatment PRA†
Hirsch 2024;[33] cohort study, Germany	130 (78 with UNS, 52 with SUP)	UNS group: female: 30 (39%); DRC after treatment: median 31·8 (IQR 18·6–81·7) mIU/L; SUP group: female: 23 (44%); DRC after treatment: median 4·9 (IQR 2·8–8·6) mIU/L	DRC 12 mIU/L	Mean 1·7 (1) years	Cross-sectional analysis	Echocardiographic parameters; blood pressure	The primary outcomes were not measured
Hundemer 2018a;[15] cohort study, USA	201 (67 with UNS, 134 with SUP)	Age: mean 58 (SD 12) years; female: 271 (45%); history of cardiovascular disease 0; unilateral PA: 54 (16%); PRA before treatment: ≤0·6 ng/mL/h in 548 (91%) (data from overall cohort with 602 patients with PA on MRAs, including those not analysed)	PRA 1·0 ng/mL/h	1–6 months	Mean 7·0 (4·7) years (up to 10 years)	Incidence of cardiovascular events; incidence of mortality; BP	aHR 0·38 (95% CI 0·19 to 0·79) for cardiovascular events;‡ aHR 0·29 (95% CI, 0·09 to 0·98) for mortality‡
Hundemer 2018b;[20] cohort study, USA	147 (43 with UNS, 104 with SUP)	Age: mean 56 (SD 12) years; female: 182 (46%); history of cardiovascular disease 63 (16%); unilateral PA: 33 (15%); PRA before treatment: ≤0·6 ng/mL/h in 360 (90%) (data from overall cohort with 400 patients with PA on MRAs, including those not analysed)	PRA 1·0 ng/mL/h	1–6 months	Mean 7·5 (4·4) years	Incidence of renal events	aHR 0·93 (95% CI 0·46 to 1·90) for renal events§
Hundemer 2018c;[16] cohort study, USA	195 (65 with UNS, 130 with SUP)	UNS group: age: mean 57 (SD 13) years; female: 28 (43%); PRA before treatment: ≤0·6 ng/mL/h in 60 (92%); SUP group: age: mean 57 (SD 12) years; female: 58 (45%); PRA before treatment: ≤0·6 ng/mL/h in 123 (95%)	PRA 1·0 ng/mL/h	1–6 months	UNS group mean 7·8 (4·9) years; SUP group mean 7·2 (4·4) years	Incidence of atrial fibrillation	aHR 1·03 (95% CI 0·54 to 2·00) for atrial fibrillation for UNS compared with essential hypertension;¶ aHR 2·55 (95% CI 1·75 to 3·71) for atrial fibrillation for SUP compared with essential hypertension¶

(Table continues on next page)

	Number of participants on MRA analysed	Key characteristics of medically treated PA population*	Cut-off for UNS or SUP	Time between targeted medication initiation and post-treatment renin measurement	Follow-up period	Reported outcomes	aHR (95% CI) for the primary outcomes (UNS *vs* SUP)
(Continued from previous page)							
Jiang 2024;[45] cohort study, China	240	Age: median 52 (IQR 46–59) years; female: 98 (41%); history of cardiovascular disease 0; unilateral PA: 0; PRA before treatment: median 0·34 (IQR 0·20–0·55) ng/mL/h; PRA after treatment: median 1·81 (IQR 1·22–2·88) ng/mL/h in UNS and median 0·50 (IQR 0·25–0·78) ng/mL/h in SUP	PRA 1·0 ng/mL/h	At least 6 months	Median 5·0 (3·0–7·7) years	Incidence of cardiovascular events; eGFR; blood pressure	aHR 0·25 (95% CI 0·08 to 0·82) for cardiovascular events‖
Katsuragawa 2023;[18] cohort study, Japan	318	Age: mean 50 (SD 9·5) years; female: 188 (59%); history of cardiovascular disease 22 (6·9%); unilateral PA: 0; PRA before treatment: <0·50 ng/mL/h in 253 (79·6%); PRA after treatment: median 1·7 (IQR 0·3–2·5) ng/mL/h in UNS and median 0·5 (IQR 0·3–0·7) ng/mL/h in SUP	PRA 1·0 ng/mL/h	At least 6 months (median 1 year)	Median 3·1 (1·0–5·8) years	eGFR; blood pressure	The primary outcomes were not measured
Kishimoto 2020;[46] cohort study, Japan	23	Age: mean 50 (SD 11) years; female: 8 (35%); history of cardiovascular disease 0; unilateral PA: 23 (100%); PRA before treatment: mean 0·8 (SD 0·6) ng/mL/h; PRA after treatment: mean 1·5 (SD 1·7) ng/mL/h	PRA 1·0 ng/mL/h	3 months	Cross-sectional analysis	Vascular function	The primary outcomes were not measured
Kobayashi 2020;[47] cohort study, Japan	746	Age: mean 54 (SD 10·7) years; female: 393 (53%); history of cardiovascular disease 39 (5·2%); unilateral PA: 0; PRA before treatment: mean 0·4 (SD 0·3) ng/mL/h	Change in PRA from pre to post-MRA initiation as a continuous variable	6 months	Cross-sectional analysis	eGFR	The primary outcomes were not measured
Kohler 2021;[34] cohort study, Germany	105 (59 with UNS, 46 with SUP)	Age: median 49 (IQR 42–58) years; female: 41 (39%); DRC before treatment: median 4·2 (IQR 2·1–8·1) mIU/L; DRC after treatment: median 32·5 (IQR 18·4–64·5) mIU/L in USP and median 5·0 (IQR 3·0–8·9) mIU/L in SUP	DRC 12 mIU/L	1 year	Cross-sectional analysis	Echocardiographic parameters; blood pressure	The primary outcomes were not measured
Kurozumi 2021;[48] cohort study, Japan	10	Age: mean 60 (SD 13) years; female: 7 (70%); PRA before treatment: mean 0·32 (SD 0·2) ng/mL/h; PRA after treatment: mean 0·94 (SD 0·51) ng/mL/h	Change in PRA from pre to post MRA initiation as a continuous variable	3 months	Cross-sectional analysis	Vascular function	The primary outcomes were not measured
Nomura 2022;[49] cohort study, Japan	1115 (Low PRA change 383, Intermediate PRA change 378, High PRA change 354)	High PRA change: age: mean 54 (SD 11) years; female: 167 (47%); unilateral PA: 35 (10%); PRA before treatment: median 0·4 (IQR 0·2–0·6) ng/mL/h; intermediate PRA change: age: mean 54 (SD 10) years; female: 238 (57%); unilateral PA: 52 (14%); PRA before treatment: median 0·3 (IQR 0·2–0·5) ng/mL/h; low PRA change: age: mean 54 (SD 11) years; female: 216 (62%); unilateral PA: 34 (9%); PRA before treatment: median 0·4 (IQR 0·2–0·6) ng/mL/h	High PRA change: change in PRA from pre to post MRA initiation ≥0·8 ng/mL/h; intermediate PRA change: ≤0·2 ng/mL/h change in PRA from pre to post MRA initiation ≤0·7 ng/mL/h; low PRA change: change in PRA from pre to post MRA initiation ≤0·1 ng/mL/h	6, 12, 36, or 60 months	Median 3·0 (1·1–5·0) years	Composite incidence of cardiovascular events and mortality; eGFR; blood pressure	For cardiovascular events, aHR 3·73 (95% CI 0·79 to 17·7) for low PRA change compared with intermediate PRA change;** aHR 5·71 (95% CI 1·28 to 25·5) for high PRA change compared with intermediate PRA change**
ParraRamirez 2024;[19] cohort study, Spain	160 (70 with UNS, 90 with SUP)	Age: mean 57 (SD 6·8) years; female: 62 (39%); history of cardiovascular disease 29 (18%); PRA before treatment: median 0·2 (IQR 0·1–0·4) ng/mL/h; PRA after treatment: mean 4·7 (SD 4·2) ng/mL/h in USP and mean 0·7 (SD 2·5) ng/mL/h in SUP	PR 1·0 ng/mL/h Or DRC 10 mIU/L	At least 4 weeks (median 1 [0·5–3·6] year)	Median 1 (0·5–3·6) year	Incidence of cardiovascular events; incidence of renal events; eGFR; blood pressure	Unadjusted HR 1·14 (95% CI 0·40 to 3·27) for cardiovascular events; unadjusted HR 1·01 (95% CI 0·27 to 3·74) for renal events

(Table continues on next page)

	Number of participants on MRA analysed	Key characteristics of medically treated PA population*	Cut-off for UNS or SUP	Time between targeted medication initiation and post-treatment renin measurement	Follow-up period	Reported outcomes	aHR (95% CI) for the primary outcomes (UNS *vs* SUP)
(Continued from previous page)							
Puar 2022;[17] cohort study, Singapore	32	Age: mean 55 (SD 11) years; female: 17 (30%); PRA before treatment: median 0·6 (IQR 0·2–2·5) ng/mL/h, PRA after treatment: median 1·3 (IQR 0·6–14) ng/mL/h (data from overall cohort with 57 patients with PA, including those undergoing adrenalectomy)	PRA 1·0 ng/mL/h	1 year	Cross-sectional analysis	Echocardiographic parameters	The primary outcomes were not measured
Saiki 2022;[50] single-arm interventional study, Japan	24 (12 with UNS, 12 with SUP)	Age: median 60 (IQR 48–74) years; female: 18 (75%); PRA after treatment: median 2·2 (IQR 1·3–4·0) ng/mL/h in USP and median 0·6 (IQR 0·4–0·8) ng/mL/h in SUP	PRA 1·0 ng/mL/h	At least 6 months (median 2 [1–4] years)	6 months	Urinary albumin excretion; eGFR; blood pressure	The primary outcomes were not measured
Satoh 2021;[51] single-arm interventional study, Japan	41 (17 with UNS, 24 with SUP)	Age: mean 50 (SD 10) years; female: 25 (57%); unilateral PA: 4 (9·1%); PRA before treatment: mean 0·49 (SD 0·51) ng/mL/h (data from overall cohort with 44 patients with PA, including those whose post-treatment renin was not measured)	PRA 1·0 ng/mL/h	3 months	Cross-sectional analysis	Blood pressure	The primary outcomes were not measured
Tezuka 2021;[36] cohort study, USA	123 (49 with UNS, 74 with SUP)	Age: median 56 (IQR 47–64) years; female: 49 (40%); history of cardiovascular disease 23 (19%); unilateral PA: 25 (19%); PRA before treatment: median 0·2 (IQR 0·1–0·6) ng/mL/h; PRA after treatment: median 2·3 (IQR 1·3–5·9) ng/mL/h in USP and median 0·3 (IQR 0·2–0·6) ng/mL/h in SUP	PRA 1·0 ng/mL/h or DRC 8·0 pg/mL	Median 4·1 (2·1–11) months	Cross-sectional analysis	eGFR	The primary outcomes were not measured
Ueda 2022;[52] cohort study, Japan	76	Age: median 50 (IQR 42–56) years; female: 39 (51%); PRA before treatment: median 0·35 (IQR 0·23–0·52) ng/mL/h; PRA after treatment: median 0·7 (IQR 0·4–1·2) ng/mL/h	PRA 1·0 ng/mL/h	1 year	Cross-sectional analysis	Echocardiographic parameters	The primary outcomes were not measured
Wu 2022;[53] cohort study, Taiwan	313 (200 with UNS, 113 with SUP)	Age: mean 58 (SD 13) years; female: 168 (54%); history of cardiovascular disease 53 (17%); unilateral PA: 313 (100%); PRA before treatment: mean 1·08 (SD 3·62) ng/mL/h	PRA 0·6 ng/mL/h	1 year	Mean 6·3 (4·0) years	Composite incidence of cardiovascular events and mortality; blood pressure	aHR 0·26 (95% CI 0·07 to 0·94) for cardiovascular events††
Yang 2025;[14] cohort study, multiple countries	1057 with post-renin but overall cohort was 1248 which included patients with only clinical data, not post-renin	Complete response: age: mean 51 (SD 11) years; female: 272 (49%); PRA before treatment: median 0·5 (IQR 0·29–0·70) ng/mL/h; DRC before treatment: median 4·1 (IQR 2·1–6·8) mIU/L; PRA after treatment: median 2·5 (IQR 1·55–4·2) ng/mL/h; DRC after treatment: median 22·6 (IQR 15–48) mIU/L; partial response: age mean 53 (SD 11) years; female: 145 (51%); PRA before treatment: median 0·2 (IQR 0·10–0·40) ng/mL/h; DRC before treatment: median 2·0 (IQR 1·6–3·3) mIU/L; PRA after treatment: median 0·7 (IQR 0·40–0·80) ng/mL/h; DRC after treatment: median 5·0 (IQR 3·0–7·0) mIU/L; absent response: age mean 51 (SD 11) years; female: 98 (46%); PRA before treatment: median 0·5 (IQR 0·23–0·60) ng/mL/h; DRC before treatment: median 4·0 (IQR 2·0–6·3) mIU/L; PRA after treatment: median 0·42 (IQR 0·20–0·60) ng/mL/h; DRC after treatment: median 2·3 (IQR 2·0–5·0) mIU/L	PRA 1·0 ng/mL/h or DRC 10 mIU/L	Median 9 (7–11) months	Cross-sectional analysis	Echocardiographic parameters; urinary albumin excretion; eGFR; blood pressure	The primary outcomes were not measured

(Table continues on next page)

	Number of participants on MRA analysed	Key characteristics of medically treated PA population*	Cut-off for UNS or SUP	Time between targeted medication initiation and post-treatment renin measurement	Follow-up period	Reported outcomes	aHR (95% CI) for the primary outcomes (UNS *vs* SUP)
(Continued from previous page)							
Yoshida 2023;[54] single-arm interventional study, Japan	26 (16 with UNS, 10 with SUP)	Age: median 52 (IQR 48–62) years; female: 14 (54%); unilateral PA: 0 ; DRC before treatment: median 2·6 (IQR 1·2–3·8) pg/ml; DRC after treatment: median 8·3 (IQR 6·3–11·3) pg/ml in USP and median 3·4 (IQR 2·8–4·0) pg/ml in SUP	DRC 5 pg/mL	6 months	Cross-sectional analysis	eGFR; blood pressure	The primary outcomes were not measured

aHR=adjusted hazard ratio. DRC=direct renin concentration. eGFR=estimated glomerular filtration rate. MRA=mineralocorticoid receptor antagonists. PA=primary aldosteronism. PAC=plasma aldosterone concentration. PRA=plasma renin activity. SUP=suppressed post-treatment renin. UNS=unsuppressed post-treatment renin. *Key population characteristics included age, sex, before history of cardiovascular disease, PA lateralisation, and PRA or DRC before and after targeted medical treatment (if available). The mean (SD) or median (IQR) is shown for continuous variables and the proportion (%) is shown for categorical variables. †Adjusted for treatment and the estimated 5-year cardiovascular disease risk score, duration of hypertension, and PAC, PRA, and systolic and diastolic blood pressure 6 months after treatment. ‡Adjusted for age, sex, race or ethnic origin, BMI, smoking status, diabetes, HbA_{1c}, atrial fibrillation, LDL cholesterol, statin use, daily aspirin use, eGFR, systolic blood pressure, diastolic blood pressure, and number of antihypertensive medications. §Adjusted for age, sex, race, history of diabetes, history of cardiovascular disease, eGFR, systolic blood pressure, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use. ¶Adjusted for age, sex, race, BMI, diabetes, eGFR, and systolic blood pressure. ||Adjusted for hypertension duration, history of diabetes, serum potassium, and defined daily doses of antihypertensive agents. **Adjusted for age, sex, BMI, eGFR at baseline. ††Adjusted for age, sex, Charlson comorbidity index, BMI, antihypertensive drugs, systemic blood pressure, diastolic blood pressure, and potassium level.

Table: **Characteristics of included studies**

interaction=0·040; figure 3, appendix pp 8–9).[19] Other subgroup analyses stratified by cut-off values of post-treatment renin (PRA ≤0·6 ng/mL per h or PRA >0·6 to <1·4 ng/mL per h) and region (Asia or non-Asia) did not reveal differences in the association by the subgroups (p values for subgroup interaction=0·43 for cut-off PRA ≤0·6 ng/mL per h *vs* >0·6–<1·4 ng/mL per h and 0·21 for Asia *vs* non-Asia; appendix p 14). A consistent result was observed in a sensitivity analysis excluding studies with high risk of bias in Domain 5 of the QUIPS tool (appendix p 15). A leave-one-out meta-analysis demonstrated a consistent trend in point estimates regardless of which study was omitted; statistical significance was not reached in any case except when the study by Parra-Ramirez and colleagues was excluded,[19] at which point the association became statistically significant and heterogeneity across studies was eliminated (appendix p 15). Regarding the incidence of renal events, a meta-analysis found no association between post-treatment renin and incidence of renal events (pooled HR 0·95 [95% CI 0·51–1·77], I^2=0%, two studies, 276 patients; very low certainty of evidence; figure 4, appendix pp 8–9, 16).[19,20] Only one study reported on the incidence of all-cause mortality after a median follow-up of 7·0 years, demonstrating that patients with unsuppressed post-treatment renin had a lower risk of death compared with those with suppressed renin (adjusted HR 0·29 [95% CI 0·09–0·98], 201 patients; low certainty of evidence; appendix pp 8–9).

For the secondary outcomes, meta-analyses were performed to assess the cross-sectional associations between post-treatment renin status and several clinical outcomes, including the proportion of left ventricular hypertrophy assessed by echocardiography, eGFR (mL/min per 1·73 m²), blood pressure (mm Hg), dose of MRAs (mg), and the proportion treated with spironolactone. All the outcomes were measured at the same time as the post-treatment renin measurement, and no covariate adjustment was made in their analyses. Post-treatment renin was not significantly associated with left ventricular hypertrophy (80 [28·3%] of 283 in unsuppressed *vs* 75 [30·6%] of 245 in suppressed, pooled OR 0·59 [95% CI 0·17 to 2·00], I^2=63%, two studies, 528 patients; very low certainty of evidence; appendix pp 9–10),[14,41] nor was it associated with eGFR (pooled mean difference –1·9 mL/min per 1·73 m² [95% CI –4·4 to 0·6], I^2=28%, seven studies, 1948 patients; very low certainty of evidence; appendix pp 9–10, 18).[14,18,19,36,45,50,54] Patients with unsuppressed post-treatment renin, compared with those with suppressed post-treatment renin, had significantly lower systolic and diastolic blood pressure (pooled mean difference –4·4 mm Hg [95% CI –6·2 to –2·6] for systolic blood pressure, I^2=42%; pooled mean difference in diastolic blood pressure –3·3 mm Hg [95% CI –4·9 to –1·6] for diastolic blood pressure, I^2=60%, ten studies, 2659 patients; very low certainty of evidence; appendix pp 10, 19–21).[14,15,18,19,33,42,45,50,53,54] The

heterogeneity observed in the meta-analyses of blood pressure was reduced in each subgroup when stratified by post-treatment renin cut-off values (appendix pp 22, 24). The association with systolic blood pressure was stronger in the subgroup with a cut-off PRA of greater than 1·4 ng/mL per h, compared with a cut-off value PRA of 0·6–1·4 ng/mL per h (p value for subgroup interaction=0·015; appendix pp 22).

Regarding treatment intensity, patients with unsuppressed post-treatment renin received higher doses of MRAs than those with suppressed post-treatment renin (pooled mean difference 3·4 mg [95% CI 0·3 to 6·4], I^2=71%, eight studies, 2149 patients; very low certainty of evidence; appendix p 27).[14,15,18,19,36,45,50,54] Additionally, seven studies involving 2026 patients reported the number of patients who used each type of MRAs,[14,15,18,19,45,50,54] in which spironolactone, eplerenone, and esaxerenone were used in 1296 patients (64%), 626 patients (31%), and 52 patients (3%), respectively. The proportion of patients who used spironolactone was higher in patients with unsuppressed post-treatment renin than those with suppressed post-treatment renin (700 [71%] of 980 patients *vs* 596 [57%] of 1046 patients, pooled OR 1·84 [95% CI 1·47 to 2·29], I^2=6%, seven studies, 2026 patients; very low certainty of evidence; appendix pp 28–29).[14,15,18,19,45,50,54]

Only one study reported adverse outcomes potentially attributable to MRA therapy, including gynaecomastia, hyperkalaemia, acute creatine elevation, irregular menses, decreased libido, rash, fatigue, light-headedness, angioedema, and frequent urination, according to post-treatment renin status.[36] No difference was observed between patients with post-treatment PRA 1·0 ng/mL per h or greater and those with post-treatment PRA less than 1·0 ng/mL per h (16 [33%] of 49 *vs* 25 [34%] of 74, p=0·64). Meta-analyses were not conducted for pulse wave velocity and urinary microalbumin excretion due to the scarcity of available studies. Further details on both primary and secondary outcomes reported in the eligible studies, including those not incorporated into the meta-analyses, are described in the appendix (pp 6–7, 13–31).

Discussion

Our systematic review and meta-analysis found that unsuppressed renin following initiation of targeted medical treatment was associated with a reduced risk of cardiovascular events and all-cause mortality, particularly when the follow-up duration was 5 years or more. By contrast, no significant association was observed for renal events, with the certainty of evidence rated as very low.

To our knowledge, this is the first systematic review to synthesise currently available evidence on the association between post-treatment renin and clinical outcomes in medically treated primary aldosteronism. The pooled hazard ratio for cardiovascular events (pooled HR 0·43 [95% CI 0·23–0·80]), which favoured patients with unsuppressed post-treatment renin, was consistent with the estimates of most studies included;[15,45,53] one study by Parra-Ramirez and colleagues, however, reported null association in contrast to the others.[19] Our leave-one-out analysis, in which the omission of the study by Parra-Ramirez and colleagues strengthened the association, also suggests a significant influence of the study on the overall pooled estimate. The reason for the conflicting result likely stems from a substantially shorter follow-up duration in the study by Parra-Ramirez and colleagues (median 1 year),[19] compared with the others (5–7 years in median or mean).[15,45,53] The difference

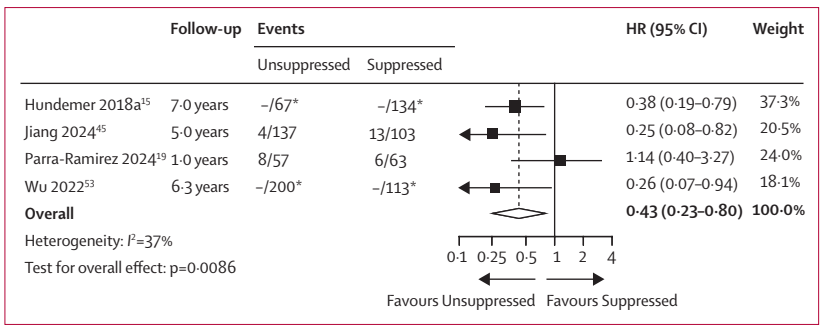

Figure 2: **Forest plot for the association between post-treatment renin status and the incidence of cardiovascular events**
HR=hazard ratio. *The number of events in each group were not reported.

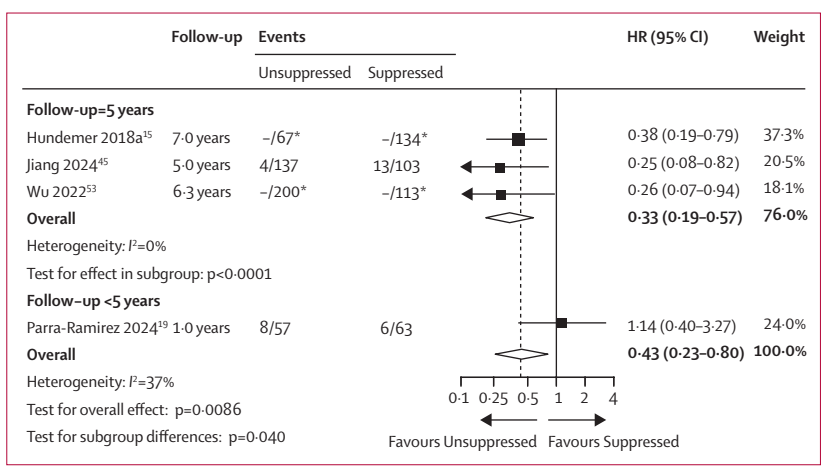

Figure 3: **Subgroup analysis stratified by follow-up duration for the association between post-treatment renin status and the incidence of cardiovascular events**
HR=hazard ratio. *The number of events in each group were not reported.

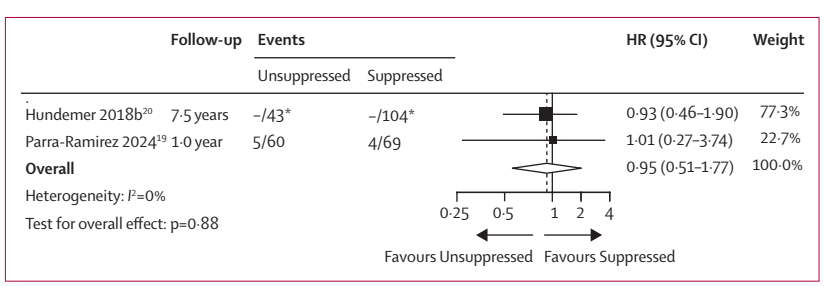

Figure 4: **Forest plot for the association between post-treatment renin status and the incidence of renal events**
HR=hazard ratio. *The number of events in each group were not reported.

in follow-up duration could also account for the low to moderate heterogeneity observed in the meta-analysis (I^2=37%). The subgroup analysis stratified by follow-up duration (≥5 years *vs* <5 years) eliminated heterogeneity (I^2=0%), underscoring the importance of sufficient follow-up time. However, as no studies included follow-up periods between 2 years and 4 years, the minimum duration required to detect a significant difference in cardiovascular outcomes between patients with unsuppressed versus suppressed post-treatment renin remains uncertain. Additionally, among the studies included in the meta-analysis for cardiovascular events, the study by Wu and colleagues included a unique population of patients with unilateral primary aldosteronism,[53] which is generally considered to demonstrate more severe clinical manifestation such as resistant hypertension and hypokalaemia.[1,2] The study also included relatively high proportion of patients on interfering medications (eg, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers) and an unusually high baseline PRA before targeted treatment (1·08 ng/mL per h among patients treated with MRAs). These factors might limit comparability with other studies. However, in our leave-one-out meta-analysis, excluding the study by Wu and colleagues did not considerably change the result. This might imply that the influence of the study on the overall pooled estimate was minimal. Nevertheless, it is necessary to interpret the result with caution.

A recent systematic review and meta-analysis by Huang and colleagues,[55] including patients with primary aldosteronism treated with MRA and those who underwent adrenalectomy, analysed the association between study-level post-treatment PRA and cardiovascular events. Their meta-analysis demonstrated that studies with mean PRA levels of 1·0 to 2·0 ng/mL per h had a lower incidence rate of cardiovascular events than those with mean PRA levels of less than 1·0 ng/mL per h. The findings of our meta-analysis revealed a similar trend using post-treatment renin status at an individual level. Our findings are also consistent with guidelines and expert recommendations to titrate MRA to achieve renin normalisation as a therapeutic goal for cardiovascular risk reduction,[1,9,11–13] however causality remains to be confirmed. Also, the possible benefit may be limited only with a long follow-up (5 years or more).

In our meta-analysis, the association between post-treatment renin and renal events was not significant, with a very low certainty of evidence. Both contributing studies had a small sample size (<150 patients each),[19,20] one of which also had short follow-up duration (median one year).[19] These factors may have led to the reduced statistical power. A separate study consisting of 318 individuals, followed up for 3·1 years, suggested a possibly favourable renal prognosis in patients with unsuppressed post-treatment renin, reporting a 0·96 mL/min/1·73m² per year slower eGFR decline in patients with unsuppressed post-treatment renin versus suppressed post-treatment renin.[18] However, this study did not report the incidence of renal events and was therefore excluded from the meta-analysis. Larger and longer-term studies are required to confirm whether unsuppressed post-treatment renin confers a renal benefit. Secondary outcomes supported the possible benefit of unsuppressed renin on renal prognosis, with unsuppressed post-treatment renin associated with lower blood pressure, which is a well-established factor in the prevention of kidney disease progression.[56] Together, these findings might suggest that normalising post-treatment renin may also improve renal prognosis through better blood pressure control. Our meta-analysis also revealed that patients with unsuppressed post-treatment renin used higher dose of MRAs than those with suppressed renin, suggesting that MRA dose up-titration is an important aspect of targeted medical treatment to improve prognosis via normalisation of post-treatment renin. Moreover, spironolactone was used more frequently in patients with unsuppressed post-treatment renin (71%) than those with suppressed post-treatment renin (57%) in our meta-analysis. This might imply that in real-world settings, the lower potency of eplerenone prevents efficient up-titration.[35] Alternatively, patients receiving eplerenone or esaxerenone could have switched from spironolactone due to adverse effects,[1,35] in which case clinicians might be more hesitant to further up-titrate the dose of eplerenone or esaxerenone, resulting in persistent renin suppression.

Our review identified only one study that included patients treated with ENaC inhibitors,[14] whereas the remaining studies exclusively evaluated MRA-treated populations. This limits the generalisability of our findings. ENaC is expressed on the principal cell in the kidney and mediates sodium reabsorption following mineralocorticoid receptor activation.[57] Considering that ENaC inhibitors block the sodium transport via ENaC which, at least partially, inhibits one of the downstream pathways of mineralocorticoid receptor activation,[58] post-treatment renin status might also serve as a useful treatment target in patients with primary aldosteronism treated with ENaC inhibitors. However, as mineralocorticoid receptors are expressed in various organs beyond the principal cell in the kidney,[58] the physiological implication of post-treatment renin might differ between MRAs and on ENaC inhibitor therapy; hence, our findings might not be directly extrapolated to patients with primary aldosteronism treated with ENaC inhibitors.

The strengths of this review include the comprehensive scope across both major clinical outcomes and relevant surrogate markers as secondary outcomes, allowing for a more detailed study of the association between post-treatment renin status and broad health outcomes. This is particularly relevant in cases where available evidence is insufficient to make a

robust conclusion as was observed in our meta-analysis for renal events. However, several limitations must be acknowledged. First, all included studies were observational in terms of the association between post-treatment renin status and outcomes, and thus residual and uncontrolled confounding remains a concern despite our risk of bias assessment and sensitivity analysis excluding high-risk studies. One potential confounder is the concurrent use of other medication that might interfere with the exposure and outcomes. For example, β-blockers, which are known to decrease plasma renin,[10] were used more frequently in the suppressed renin group than the unsuppressed renin group in one of the studies included in the meta-analysis for cardiovascular events,[45] and a similar trend was observed in another study.[19] This implies the possibility of an imbalance in the medications used between the groups; most of the studies in the meta-analyses for the primary outcomes did not control for this except for one study.[53] Treatment adherence is another potential confounder. Our meta-analysis found that MRA dose was lower in patients with suppressed post-treatment renin than those with unsuppressed renin, although it is unclear whether the MRA dose reported in each study represented the amount actually taken by patients or the amount prescribed by clinicians. Thus, the patients with suppressed post-treatment renin might have been less adherent not only to MRA and also to non-MRA or ENaC-inhibitor antihypertensive agents or non-antihypertensive treatment such as lifestyle modification, potentially contributing to poorer clinical outcomes. Therefore, the findings should be interpreted with caution given the risk of residual confounding. Second, as post-treatment renin status is an exposure but not an intervention, causality cannot be established.[59] Prospective trials are needed to confirm whether renin-guided titration of MRAs, and possibly ENaC inhibitors, improves outcomes. Indeed, one such trial in patients with primary aldosteronism is underway, comparing clinical outcomes between renin-guided and renin-blinded groups (NCT06108427).[60] Third, there is a possibility of sparse data bias,[61,62] as several of the studies had few outcome events relative to the number of covariates adjusted for. An individual participant data meta-analysis could better address this limitation.[62] Fourth, the studies included in this review were heterogeneous in several aspects. Post-treatment renin was defined as suppressed or unsuppressed using different cut-off values, and the timing and frequency of post-treatment renin measurements were not consistent across studies. Therefore, caution is needed when interpreting the results of meta-analyses that combine such heterogeneous data. In our subgroup analysis of blood pressure outcomes, stratification by post-treatment renin (ie, PRA ≤0·6 ng/mL per h, PRA >0·6 to <1·4 ng/mL per h, or PRA ≥1·4 ng/mL per h) reduced heterogeneity within subgroups. This finding suggests that the association between post-treatment renin and blood pressure might depend on the cut-off value used.

Geographical variation is another potential source of heterogeneity. Although most included studies were conducted in Asia, subgroup analyses by region for several outcomes did not show obvious differences in the association between post-treatment renin and outcomes by region. Additionally, no studies assessed the effect of supraphysiological renin levels. One study reported an increased risk of cardiovascular events with a large PRA change (≥0·8 ng/mL per h) following MRA initiation (adjusted HR 5·71 [95% CI 1·28–25·5]),[49] but the wide 95% CI and low number of events suggest a high risk of overestimation due to the sparse data bias.[61] Furthermore, all the included studies analysed post-treatment renin measured at a single point in time, and data are lacking regarding the optimal frequency and duration of renin testing after the initiation of targeted medical therapy. Given the variability of renin levels within individuals,[31] a single measurement might not reflect long-term biochemical control. This raises the possibility of misclassification bias and limits the ability of this review to determine the optimal frequency and duration of post-treatment renin assessment. Future research should evaluate the clinical significance of excessive renin increase and establish evidence-based recommendations for the optimal timing, frequency, and duration of post-treatment monitoring. Finally, we did not search grey literature sources and trial registries, which could introduce publication bias or small-study effects. Although the funnel plots of studies included in the meta-analyses for the primary outcomes did not appear obviously asymmetrical, the small number of studies precluded statistical tests for asymmetry, and therefore the possibility of publication bias or small-study effects cannot be ruled out.

In conclusion, our systematic review and meta-analysis demonstrated that unsuppressed post-treatment renin following targeted medical therapy for primary aldosteronism was associated with reduced risk of cardiovascular events and mortality. These findings might support the importance of achieving post-treatment renin normalisation as a key therapeutic goal in targeted medical treatment of primary aldosteronism. Medication titration to normalise renin might improve clinical outcomes, although prospective trials are needed.

Contributors

SK and JY conceptualised the study and designed the methods. SK, PJF, and JY wrote the protocol. SK, MVL, and JY assessed study eligibility and risk of bias of each study. SK and MVL extracted data from included studies and verified the data. SK conducted data analyses, and SK, MVL, and JY verified the reported results. All the authors had full access to all the data in the study. SK wrote the original draft, and all the authors contributed to reviewing and editing the subsequent drafts. All authors accept responsibility for the decision to submit the manuscript for publication. This study was supervised by JY and PJF.

Declaration of interests
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Data sharing
Data collected for the study (ie, data extracted from the included studies for our review and meta-analysis) will be made available to others upon reasonable request after the publication of the current study, if all the authors provide permission.

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References
1 Reincke M, Bancos I, Mulatero P, Scholl UI, Stowasser M, Williams TA. Diagnosis and treatment of primary aldosteronism. *Lancet Diabetes Endocrinol* 2021; **9:** 876–92.
2 Turcu AF, Yang J, Vaidya A. Primary aldosteronism—a multidimensional syndrome. *Nat Rev Endocrinol* 2022; **18:** 665–82.
3 Libianto R, Russell GM, Stowasser M, et al. Detecting primary aldosteronism in Australian primary care: a prospective study. *Med J Aust* 2022; **216:** 408–12.
4 Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2018; **6:** 41–50.
5 Monticone S, Sconfienza E, D'Ascenzo F, et al. Renal damage in primary aldosteronism: a systematic review and meta-analysis. *J Hypertens* 2020; **38:** 3–12.
6 Sechi LA, Novello M, Lapenna R, et al. Long-term renal outcomes in patients with primary aldosteronism. *JAMA* 2006; **295:** 2638–45.
7 Inoue K, Naito T, Fuji R, et al, and the BioBank Japan. Primary aldosteronism and risk of cardiovascular outcomes: genome-wide association and mendelian randomization study. *J Am Heart Assoc* 2024; **13:** e034180.
8 Hundemer GL, Leung AA, Kline GA, Brown JM, Turcu AF, Vaidya A. Biomarkers to guide medical therapy in primary aldosteronism. *Endocr Rev* 2024; **45:** 69–94.
9 Naruse M, Katabami T, Shibata H, et al. Japan Endocrine Society clinical practice guideline for the diagnosis and management of primary aldosteronism 2021. *Endocr J* 2022; **69:** 327–59.
10 Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2016; **101:** 1889–916.
11 Tseng CS, Chan CK, Lee HY, et al, and the TAIPAI Study Group. Treatment of primary aldosteronism: clinical practice guidelines of the Taiwan Society of Aldosteronism. *J Formos Med Assoc* 2024; **123** (suppl 2)**:** S125–34.
12 Faconti L, Kulkarni S, Delles C, et al. Diagnosis and management of primary hyperaldosteronism in patients with hypertension: a practical approach endorsed by the British and Irish Hypertension Society. *J Hum Hypertens* 2024; **38:** 8–18.
13 Umemura S, Arima H, Arima S, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res* 2019; **42:** 1235–481.
14 Yang J, Burrello J, Goi J, et al. Outcomes after medical treatment for primary aldosteronism: an international consensus and analysis of treatment response in an international cohort. *Lancet Diabetes Endocrinol* 2025; **13:** 119–33.
15 Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. *Lancet Diabetes Endocrinol* 2018; **6:** 51–59.
16 Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Incidence of atrial fibrillation and mineralocorticoid receptor activity in patients with medically and surgically treated primary aldosteronism. *JAMA Cardiol* 2018; **3:** 768–74.
17 Puar TH, Cheong CK, Foo RSY, et al. Treatment of primary aldosteronism and reversal of renin suppression improves left ventricular systolic function. *Front Endocrinol (Lausanne)* 2022; **13:** 916744.
18 Katsuragawa S, Goto A, Shinoda S, et al. Association of reversal of renin suppression with long-term renal outcome in medically treated primary aldosteronism. *Hypertension* 2023; **80:** 1909–20.
19 Parra Ramírez P, Martín Rojas-Marcos P, Paja Fano M, et al, and the Findings from the SPAIN-ALDO Registry. Renin as a biomarker to guide medical treatment in primary aldosteronism patients. *High Blood Press Cardiovasc Prev* 2024; **31:** 43–53.
20 Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Renal outcomes in medically and surgically treated primary aldosteronism. *Hypertension* 2018; **72:** 658–66.
21 Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021; **372:** n160.
22 The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. 2024. https://training.cochrane.org/handbook/current (accessed Sept 20, 2024).
23 Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ* 2019; **364:** k4597.
24 Veritas Health Innovation. Covidence systematic review software. Covidence. https://www.covidence.org/ (accessed April 15, 2024).
25 Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; **158:** 280–86.
26 Yang J, May Gwini S, Beilin LJ, et al. Relationship between the aldosterone-to-renin ratio and blood pressure in young adults: a longitudinal study. *Hypertension* 2021; **78:** 387–96.
27 Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline for the management of patients with acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2025; **151:** e771–862.
28 Rocchini AP, Katch VL, Grekin R, Moorehead C, Anderson J. Role for aldosterone in blood pressure regulation of obese adolescents. *Am J Cardiol* 1986; **57:** 613–18.
29 Bochud M, Nussberger J, Bovet P, et al. Plasma aldosterone is independently associated with the metabolic syndrome. *Hypertension* 2006; **48:** 239–45.
30 Fan Y, Wu M, Li X, et al. Potassium levels and the risk of all-cause and cardiovascular mortality among patients with cardiovascular diseases: a meta-analysis of cohort studies. *Nutr J* 2024; **23:** 8.
31 Ng E, Gwini SM, Libianto R, et al. Aldosterone, renin, and aldosterone-to-renin ratio variability in screening for primary aldosteronism. *J Clin Endocrinol Metab* 2022; **108:** 33–41.
32 Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum aldosterone concentration, blood pressure, and coronary artery calcium: the multi-ethnic study of atherosclerosis. *Hypertension* 2020; **76:** 113–20.
33 Hirsch A, Adolf C, Stüfchen I, et al. NT-proBNP levels in patients with primary hyperaldosteronism and autonomous cortisol cosecretion. *Eur J Endocrinol* 2024; **191:** 444–56.
34 Köhler A, Sarkis AL, Heinrich DA, et al. Renin, a marker for left ventricular hypertrophy, in primary aldosteronism: a cohort study. *Eur J Endocrinol* 2021; **185:** 663–72.
35 Funder JW. Mineralocorticoid receptor antagonists: emerging roles in cardiovascular medicine. *Integr Blood Press Control* 2013; **6:** 129–38.
36 Tezuka Y, Turcu AF. Real-world effectiveness of mineralocorticoid receptor antagonists in primary aldosteronism. *Front Endocrinol (Lausanne)* 2021; **12:** 625457.
37 Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14:** 135.

38 Foroutan F, Guyatt G, Zuk V, et al. GRADE guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol* 2020; **121:** 62–70.

39 Adler GK, Stowasser M, Correa RR, et al. Primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2025: **110:** 2453–95.

40 Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015; **350:** h870.

41 Aune A, Gerdts E, Kokorina M, et al. Persistent cardiac organ damage in surgically and medically treated primary aldosteronism. *J Hypertens* 2022; **40:** 1204–11.

42 Chen ZW, Pan CT, Liao CW, et al. Implication of MR activity in posttreatment arterial stiffness reversal in patients with primary aldosteronism. *J Clin Endocrinol Metab* 2023; **108:** 624–32.

43 Chen ZW, Liao CW, Pan CT, et al, and the TAIPAI Study Group. Reversal of arterial stiffness in medically and surgically treated unilateral primary aldosteronism. *J Hypertens* 2024; **42:** 538–45.

44 Haze T, Hirawa N, Yano Y, et al. Association of aldosterone and blood pressure with the risk for cardiovascular events after treatments in primary aldosteronism. *Atherosclerosis* 2021; **324:** 84–90.

45 Jiang Y, Zhou L, Zhang C, et al. Suppressed renin status is a risk factor for cardiocerebrovascular events in bilateral primary aldosteronism treated with mineralocorticoid receptor antagonists. *Endocr Pract* 2024; **30:** 1180–87.

46 Kishimoto S, Oki K, Maruhashi T, et al. A comparison of adrenalectomy and eplerenone on vascular function in patients with aldosterone-producing adenoma. *J Clin Endocrinol Metab* 2020; **105:** 3474–85.

47 Kobayashi Y, Haze T, Yano Y, et al, and the JPAS/JRAS Study Group. Associations between changes in plasma renin activity and aldosterone concentrations and changes in kidney function after treatment for primary aldosteronism. *Kidney Int Rep* 2020; **5:** 1291–97.

48 Kurozumi A, Okada Y, Tanaka Y. Eplerenone improves vascular endothelial function in patients with primary aldosteronism: a pilot study. *J UOEH* 2021; **43:** 379–84.

49 Nomura M, Kurihara I, Itoh H, et al, and the JPAS/JRAS Study Group. Association of cardiovascular disease risk and changes in renin levels by mineralocorticoid receptor antagonists in patients with primary aldosteronism. *Hypertens Res* 2022; **45:** 1476–85.

50 Saiki A, Otsuki M, Tamada D, et al. Increased dosage of MRA improves BP and urinary albumin excretion in primary aldosteronism with suppressed plasma renin. *J Endocr Soc* 2021; **6:** bvab174.

51 Satoh F, Ito S, Itoh H, et al. Efficacy and safety of esaxerenone (CS-3150), a newly available nonsteroidal mineralocorticoid receptor blocker, in hypertensive patients with primary aldosteronism. *Hypertens Res* 2021; **44:** 464–72.

52 Ueda T, Tsurutani Y, Osada J, et al. Comparison of echocardiographic changes between surgery and medication treatment in patients with primary aldosteronism. *J Am Heart Assoc* 2022; **11:** e023813.

53 Wu VC, Wang SM, Huang KH, et al. Long-term mortality and cardiovascular events in patients with unilateral primary aldosteronism after targeted treatments. *Eur J Endocrinol* 2021; **186:** 195–205.

54 Yoshida Y, Fujiki R, Kinoshita M, et al. Importance of dietary salt restriction for patients with primary aldosteronism during treatment with mineralocorticoid receptor antagonists: the potential importance of post-treatment plasma renin levels. *Hypertens Res* 2023; **46:** 100–07.

55 Huang CW, Huang TY, Yang YF, et al. Major adverse cardiovascular events in primary aldosteronism after adrenalectomy or mineralocorticoid receptor antagonist treatment: a systematic review and meta-analysis. *J Am Heart Assoc* 2025; **14:** e038714.

56 Kidney DISEASE: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int* 2024; **105:** S117–314.

57 Palmer BF. Regulation of potassium homeostasis. *Clin J Am Soc Nephrol* 2015; **10:** 1050–60.

58 Alfarano M, Marchionni G, Costantino J, et al. Aldosterone-related cardiovascular disease and benefits of mineralocorticoid receptor antagonists in clinical practice. *JACC Adv* 2025; **4:** 101762.

59 Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond)* 2008; **32** (suppl 3)**:** S8–14.

60 Goupil R. Renin-guided therapy with mineralocorticoid receptor antagonists in primary aldosteronism - feasibility study (RETAME-PA). 2024. https://clinicaltrials.gov/study/NCT06108427 (accessed Aug 6, 2025).

61 Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ* 2016; **352:** i1981.

62 Richardson DB, Cole SR, Ross RK, Poole C, Chu H, Keil AP. Meta-analysis and sparse-data bias. *Am J Epidemiol* 2021; **190:** 336–40.

Letter to confirm the applicant's role in the study

Applicant name: Sho Katsuragawa

Relevant publication:

Post-treatment renin status and cardiovascular, renal, and mortality outcomes in medically treated primary aldosteronism: a systematic review and meta-analysis

Sho Katsuragawa, Minh V Le, Peter J Fuller, Jun Yang

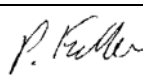
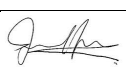
The Lancet Diabetes & Endocrinology. 2025 Dec;13(12):1041-1053.

To the ESA Young Investigator Scientific Article Award Selection Committee:

As the Head of Endocrine Hypertension Group at Hudson Institute of Medical Research, I can confirm that the applicant, Dr Sho Katsuragawa, contributed significantly to the above publication.

Dr Katsuragawa conceptualised the study, and took the leading role in designing the study, including the formulation of the research question, the development of the study protocol, and designing the methods. He also led the processes of the systematic review and meta-analysis, including developing search strategies, title, abstract and full-text screening (assisted by Dr Minh Le), data extraction, risk of bias assessment, statistical analysis, and assessing certainty of evidence. Additionally, the applicant led manuscript writing and creating tables and figures. After peer review of the journal, he rigorously addressed all the comments and suggestions from five reviewers including a statistical reviewer.

All the co-authors confirm that the above statement is a true and accurate description of the applicant's contribution to this study.

Name (printed)	Affiliation	Signature	Date
Sho Katsuragawa	Hudson Institute of Medical Research		08/07/2026
Minh V Le	Royal Melbourne Hospital		09/07/2026
Peter J Fuller	Hudson Institute of Medical Research		15/07/2026
Jun Yang	Hudson Institute of Medical Research		08/07/2026

Yours sincerely,

Prof Jun Yang, MBBS FRACP PhD
Head, Endocrine Hypertension Group, Hudson Institute of Medical Research